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MEAN ARTERIAL PRESSURE AND CEREBRAL BLOOD FLOW REGRESSION FOR PREDICTION OF CENTRAL NERVOUS SYSTEM OXYGEN TOXICITY

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TECHNICAL REVIEW AND APPROVAL
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The experiments reported herein were conducted according to the principles set forth in the current edition of the "Guide for the Care and Use of Laboratory Animals," Institute of Laboratory Animals Resources, National Research Council.

This technical report has been reviewed by the NMRC scientific and public affairs staff and is approved for publication. It is releasable to the National Technical Information Service where it will be available to the general public, including foreign nations.

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One toxic effect of hyperbaric oxygen (HBO) exposure is tonic-clonic seizures. To assess the association between seizure onset, mean arterial pressure (MAP) and cerebral blood flow (CBF), male Yorkshire swine were chronically instrumented to measure those parameters during exposure to 3, 4, 5 or 6 atmosphere absolute (ATA) on 100% oxygen. Seizure latency differed significantly as a function of pressure ($P < 0.05$). The increase in MAP and CBF correlated with seizure latency and multiple regression analysis demonstrated that MAP and CBF jointly predict seizure latency. These results demonstrate that a measurable increase in MAP and CBF may be a useful predictive tool, which may improve the safety of diving operations and clinical treatments requiring HBO.

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ABSTRACT

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INTRODUCTION

One risk of breathing pure oxygen, especially at elevated pressures, is the development of central nervous system (CNS) toxicity, including the onset of generalized tonic clonic seizures. Professionals involved in diving operations are often required to utilize 100% oxygen in a closed-circuit breathing apparatus. Hyperbaric oxygen (HBO)-induced seizures in an open environment are potentially fatal. The risk of such seizures has imposed exposure limits of 15.2 meters for 10 min in military diving operations. In addition to diving operations, HBO is a treatment modality for a number of clinical conditions, including carbon monoxide poisoning, decompression sickness and lower extremity wound care (2). Developing a method to prevent or predict seizures would enhance the safety of all situations that require HBO exposures.

The exact mechanism for HBO-induced CNS toxicity is not completely understood, but an elevated partial pressure of oxygen in the brain is one possible explanation (4, 22, 23). Evidence from the literature indicates that, in the rodent, increases in mean arterial pressure (MAP) and cerebral blood flow (CBF) precede the seizure event and may actually serve to predict seizure onset (8, 12, 18). Similarly, regional increases in CBF appear to occur prior to the onset of electrical seizure activity in non-HBO human seizure studies (1, 3). Despite evidence for such changes in the rodent, it is unknown whether such changes occur and may be predictive in a large animal model. Such a model would be useful for future mechanistic studies of HBO-induced CNS toxicity.

The present study was conducted to determine whether a large animal model could be used to investigate mechanisms of HBO-induced CNS toxicity. Specifically, we sought to develop a swine model with the goal of evaluating the relationship between MAP and CBF as possible predictors of CNS oxygen toxicity.

METHODS

All experiments reported here were approved by the Naval Medical Research Center Institutional Animal Care and Use Committee and were conducted according to the principles set forth in the *Guide for the Care and Use of Laboratory Animals*, Institute of Laboratory Animal Resources, National Research Council, National Academy Press, 1996.

Surgery

Male Yorkshire swine (n = 68, 19.0 ± 1.8 Kg) were sedated with ketamine HCl (Ketaject: 100 mg/ml, Phoenix Pharmaceutical, Inc., St. Joseph, MO) at 30 mg/kg and given atropine sulfate (1/120 grain, Phoenix Pharmaceutical, Inc., St. Joseph, MO) at 0.4 mg/kg, i.m. to prevent excessive salivation. General anesthesia was induced with acepromazine (1.5 mg/kg, i.v.) and 5% sodium pentothal (7.5 mg/kg, i.v.) through an aural vein catheter. The surgical plane of anesthesia was maintained through bolus doses of 5% sodium pentothal (2.5 mg/kg) based on movement and the presence of a palpebral reflex. Swine were intubated with an endotracheal tube and permitted to breath spontaneously during the surgical procedure. They were arranged on a circulating warm water bath blanket connected to a heating pad for body temperature maintenance; the temperature was monitored throughout the procedure with a rectal thermistor probe.

Lactated-Ringers solution (~50 ml/hr) was administered intravenously over the course of the surgery. All surgeries were performed using sterile technique.

Catheterization of the femoral artery was achieved using the purse-string technique, which was developed in-house (Forcino and Clark, unpublished data). Briefly, an 8 cm incision was made through the skin above and parallel to the femoral artery, beginning distally from the femoral triangle. The muscle planes and surrounding connective tissue were separated and 4 cm of the artery was isolated. A silk suture was used to perform 3-4 mm insertions diagonally in a diamond pattern in the tunica media portion of the vessel wall. A small incision was made in the center of the diamond and 8 cm of the tygon catheter (I.D. = 0.254 cm, O.D.= .229 cm) filled with heparizined saline (1000 U/ml) was placed in the vessel; the distal and proximal ends were occluded by silk suture. The tygon catheter was fitted with a tygon tubing sheath at 9 cm (I.D.= 0.254 cm, O.D.= 0.457 cm) and secured with silk suture. The purse-string was pulled tightly and tied down to close the vessel wall around the catheter; the suture was secured around the sheath. The catheter was anchored several times in the surrounding muscle and fascia and then run subcutaneously to an exit incision on the back using a trocar. Common suture techniques completed the procedure. The swine was fitted with a pocketed vest that covered the back incision and secured the exposed portion of the catheter.

The incision for placing the ultrasonic Doppler (USD) flow probe was 7 cm long, 2 cm anterior to the angle of the mandible and 1.5 cm lateral to the midline over the right common carotid. After isolating the bifurcation of the common carotid and ligating the external carotid, a 3.5 mm diameter, 20 MHz, USD hard epoxy cuff probe (Harvard Apparatus, Holliston MA) was placed around the common carotid 1 cm proximal to the

bifurcation. It was tied in with silk suture threaded through holes in the cuff lip and used to estimate internal carotid flow. The probe was anchored to muscle and fascia and the leads were run subcutaneously to a 1 cm incision on the back using a trocar. The tissues were closed as described above for the femoral artery catheterization, with the externalized portions of the leads secured in the vest pocket.

Post Surgery

Animals were administered 0.2 ml Prednisolone (50 mg/ml, i.m.) immediately following surgery and at 22 h and 30 h post surgery. The femoral artery catheter was evacuated twice daily, and the line was filled with 1,000 U/ml heparin. Rectal temperature, heart rate, respiration rate, and body mass were measured each day for at least 2 and at most 3 days. In addition, swine were monitored to confirm weight bearing and locomotion in all four limbs and checked for differing skin temperatures between hind feet to ensure that blood flow to the hind limb was not compromised.

Swine were housed singly in a cage, fed standard pig chow at 2% of body mass per day to maintain a gradual weight increase. Water was provided *ad libitum*, and all animals were maintained on a 12 h light/dark cycle. To prepare the animal for HBO exposure, each one was placed in a modified Panepinto sling (Charles River, Wilmington, MA) and fitted with a hood bearing a neoprene neck dam through which either air or oxygen could be supplied. Each animal was then positioned inside the controlled hyperbaric chamber (Maine Technologies, Inc. Hatfield, PA), and the chamber was flushed with air for 10 min to simulate the sound during chamber compression. To confirm that the flow probe was measuring a change in CBF, all animals underwent a carbon dioxide (CO_2) challenge one day prior to the exposure, and changes in CBF were

evaluated. Animals not demonstrating any change were eliminated from the CBF portion of the study.

HBO Exposure

Animals were connected to an electroencephalograph (Model 8-10 Grass Instruments, West Warwick, RI), USD flow monitor, and Gould P23 pressure transducer (Cleveland, OH) on the day of the exposure. Once inside the hyperbaric chamber, swine were monitored for a 10 min control period on air at 1 atmosphere absolute (ATA). Following the control period, the chamber was pressurized to 3, 4, 5, or 6 ATA on air. After a 10 min period of equilibration in hyperbaria on air, the breathing medium was switched to 100% oxygen, and the swine were observed for signs and symptoms of CNS oxygen toxicity. Animals that did not seize after 100 min of exposure, or those that were brought up early for technical difficulties, were eliminated from the study (n=5).

Instrumentation/Data Collection/Statistical Analyses

Analogue signals for CBF, MAP, O_2, and CO_2 were filtered and displayed through a custom data acquisition system. Briefly, the voltage signal from each instrument (pressure transducer, ultrasonic Doppler, oxygen and carbon dioxide meter) was routed through an analogue to digital (A/D) converter (ATMIO-16L9, National Instrument Company, Austin, TX) to a 386DX IBM compatible PC to convert the voltage output to a digital signal. Each instrument's voltage signal was calibrated with a known quantity to determine actual numerical value measured. The data were recorded at 10Hz in a binary format, which was converted into a raw data file and averaged into 2-second intervals following completion of data recording. All results are expressed as mean ± 1 SD. Differences between groups were analyzed using a Kruskal Wallis or Mann-Whitney

Test, as appropriate, and a Bonferroni correction test was employed for multiple comparisons. In addition, a correlation z-test was performed to determine the correlation between the first increase of both MAP and CBF to seizure latency. Finally, multiple regression techniques were used to determine predictive value of CBF and MAP on seizure latency, and an F-test was used to determine significance of nested models.

RESULTS

Of the 68 animals used in the study, we successfully measured the responses of MAP and CBF from 55 and 55 animals, respectively, and 49 animals had both successful MAP and CBF measured concurrently.

Explanations for responses not obtained included: occluded catheter, lack of response to CO_2 challenge, post surgical infection, and mechanical apparatus failure.

The characteristic response of one swine at 6 ATA on 100% oxygen is presented in Figure 1. Surface control measurements were taken for 10 min prior to compression (C). During compression and equilibration (E), MAP fell below the surface control value. After switching to oxygen (O), MAP was maintained at a constant level for about 10 min, but then slowly increased beyond surface control values prior to seizure (S). CBF initially decreased upon oxygen exposure and then increased beyond surface control values prior to seizure.

The times to seizure at the various exposures, as determined by observation and electroencephalographic (EEG) discharges ranged from 73.6 ± 20.5 min (n=8), 27.7 ± 12.9 min (n=19), 18.7 ± 8.2 min (n=19), and 15.3 ± 5.0 min (n=17) for the 3, 4, 5 and 6 ATA exposures, respectively. There was a significant difference in seizure latency

between 4 and 5 ATA ($P < 0.05$, Bonferroni multiple comparison test) and between 3 and 4 ATA ($P < 0.05$), but no difference in latency between 5 and 6 ATA.

To determine the time to the first increase in MAP and CBF, the upper 95% confidence intervals (CI) were calculated from surface control measurements taken prior to exposure (time prior to compression or "C") as shown in Figure 1. The upper 95% CI were then compared to averages of 2 min intervals during the experimental period. When the mean of the 2 min window differed significantly from the upper 95% CI of the surface control measurement, an increase in both MAP and CBF were considered to have occurred. There was a significant difference between the time to the first increase among the 4 groups, with MAP at 3 ATA significantly higher than all other pressures ($P < 0.05$). No significant differences between the times to first increase were noted for the 4, 5, and 6 ATA exposures (Figure 2A). Similar results were seen for the time to first increase in CBF; the time for the 3 ATA exposure was significantly higher ($P < 0.05$) than all other pressures (Figure 2B). Figures 2A and 2B depict the relationship between time to first increase and seizure latency, with actual time for both MAP and CBF listed in Table 1.

Correlations between the time to first increase in CBF and MAP and seizure latency were examined. Figure 3A shows the association between the first increase of MAP and seizure latency, and Figure 3B presents the pattern for CBF. A Cox proportional hazard regression model, including the animals that did not seize after 100 min at 3 ATA, suggested that ambient pressure, time to first increase in MAP and CBF were important variables that explained the seizure latency ($P < 0.05$, $n = 54$). To predict the seizure latency, a multiple regression model was developed, combining ambient

pressure and the time to first increase in MAP and CBF as independent variables and seizure latency as a dependent variable. The best regression model was:

$$\text{Seizure Latency} = \text{MAP} \cdot 0.449 + \text{CBF} \cdot 0.528 - P_{amb} \cdot 54.7 + P_{amb}^2 \cdot 5.11$$

(r^2=0.906, n = 49), and predicted seizure latency with an absolute difference of 4.8 min (Figure 4).

DISCUSSION

One of the hallmarks of HBO-induced seizures, as well as some experimental seizure models, is an increase in CBF prior to seizure. Chavko et al. (8) demonstrated a significant correlation ($r = 0.8$, $P<0.01$) between the time of seizure and the time of CBF increase in a rat HBO exposure model. Artificially ventilated rats also demonstrated a similar pattern at 5 ATA 100% oxygen, wherein the time of increase in CBF strongly correlated with seizure onset (12). Prior to this study, larger animals had not been studied under HBO conditions, and it was important to determine if the correlation seen in rodents between time of seizure and the time of CBF increase could be detected. If so, changes in CBF may be used as a predictor variable during HBO exposures to prevent seizures. Swine have well-recognized anatomic and physiological similarity to humans, and their utility in biomedical research models has been well recognized (19). In recent years they have been used successfully to study a variety of diving-related conditions (7, 17) and have been used as a model to study seizures (21). They are common domestic animals, and the use of matched littermate pairs from a closed breeding colony reduces genetic variability. These facts, combined with their ease of handling, make them very

useful in hyperbaric experimentation. Unlike previous rodent models, methods to adequately measure CBF in awake, unanesthetized swine were limited. This model utilized ultrasonic Doppler as a measure of CBF velocity. Studies using ultrasonographic imaging and pulsed doppler in exercising men demonstrated that increases in CBF velocity, measured in the ipsilateral middle cerebral artery, were similar to changes in flow in both the internal carotid artery and the common carotid artery (11), suggesting that our measurement of internal carotid artery flow is similar to changes in CBF velocity.

Our study confirmed that the correlation between time of seizure and time of CBF increase is distinct in a large animal model, demonstrating that an increase in the CBF is a predictive indicator of seizure onset (Fig. 3B and 4). Consequently, this first CBF increase, ranging from 49 min at 3 ATA to 7 min at 6 ATA, allows sufficient time to decrease exposure and prevent a CNS event. The difference between time to first increase of CBF at 3 ATA compared with 4, 5, or 6 ATA is merely a reflection of the increased time to seizure and still reflects the overall 31-43% of seizure latency.

The increase in blood flow prior to seizure also has been noted in a variety of other seizure models. For example, Pentylenetertrazol (PTZ) as well as kainic acid (KA) seizure models show an increase in blood flow prior to seizure (14, 24). In humans, regional CBF appears to increase several minutes prior to the onset of epileptic temporal lobe electrical discharges (1, 3). Our study replicates the pattern of initial CBF decrease immediately upon HBO exposure followed by an increase beyond control levels as seen in rodent models (8, 10).

In addition to CBF changes, we demonstrated a possible predictive value between the first increase in MAP and seizure latency (Fig. 3A). Again, the increase in 3 ATA time to first increase of MAP compared to 4, 5, or 6 ATA reflects the increase in overall time to seizure at 3 ATA. Moreover, the results of this study indicate that MAP is the least variable of these two physiological variables: it reliably predicted time to seizure at 57-61% of seizure latency, regardless of pressure, allowing sufficient notification time ranging from 29 min at 3 ATA and 7 min at 6 ATA. Rats exposed to 5 ATA and 100% oxygen displayed a similar pattern of continuously rising MAP until time to seizure (8, 12). Torbati et al. (23) also showed that blood pressure in rats increased during exposure to HBO (5 and 7 ATA), with maximum blood pressure occurring a few minutes before the first electrical discharge. MAP was increased 120% over control in ventilated rats 20 min after exposure to 5 ATA, with an average seizure latency of 37 min (18). In a non-seizure HBO exposure, MAP and systolic blood pressure increased significantly above control in rats exposed to 4.9 ATA for 1 h (5). A similar increase in MAP was noted prior to the onset of seizure in the PTZ seizure model (15). Thus, MAP, as noted for CBF, appears to be a reliable marker for an impending seizure. However, it is not clear if neural damage occurred prior to the first increase in MAP or CBF and it would be important that future studies determined if damage is absent before or just after this increase if this method is to be useful.

The mechanisms whereby alterations in CBF and MAP are induced remain unknown, although it is possible that MAP may be responsible for the increase in CBF. Prior to seizure onset MAP exceeded the autoregulatory range of CBF (50-150 mmHg) in some swine, and this could account for the vasodilation of the cerebral vasculature. An

association between increasing MAP and alterations in CBF in some seizure models has led to the suggestion that a loss of autoregulation may be important (9, 12, 16). However, in our study, the first increase of CBF often preceded the increase in MAP.

One of the primary factors responsible for mediating CBF is nitric oxide (NO). Inhibition of NO synthesis during hyperbaric O_2 exposure increased the time to first seizure in rats (13). Pre-treating rats with L-NAME, a competitive nitric oxide synthase (NOS) inhibitor in HBO and some KA seizure models, has resulted in decreased CBF and increased seizure latency as compared to controls (8, 20). Several studies suggest an HBO-induced increase in NO production. Demchenko et al. (10) demonstrated that NO production increased as a result of HBO exposure, and Bernareggi et al. (6) found inducible NOS in plasma leakage of the rat trachea following exposure to HBO. Yet, others have found a timely increase in NO metabolite production that was related to the increase in CBF prior to HBO seizure in rats (18). Oury et al. (13) suggested several possible mechanisms by which NO could contribute to CNS oxygen toxicity. One possibility is that NO works as a vasodilatory and increased levels of NO reverse the vasoconstrictor effect of O_2, increasing brain oxygenation (13). Thus, prevention of NO-induced vasodilatation could prevent the increase in CBF associated with seizures. This is consistent with the data from this study where there was an initial decrease in the CBF and a slight increase in the MAP after the gas switch from air to O_2 (Fig. 1), indicative of cerebral vasoconstriction. The subsequent increase in both MAP and CBF prior to the seizure suggests vasodilation of the cerebral vasculature that increases the oxygenation.

Regardless of the mechanism by which CBF and MAP may affect seizure latency, these results clearly demonstrate that both parameters increase prior to the onset of

seizure. Regression analysis indicated that these parameters, together with the ambient pressure, can adequately predict seizure latency. Our study demonstrates that seizure latency was predicted with an absolute difference of 4.8 min. The changes in the physiological patterns for CBF and MAP during exposure to 100% oxygen may serve as reliable indicators of CNS toxicity. The developments of a non-invasive means to assess oxygen toxicity would reduce the probability of a CNS seizure during operational diving and enhance the safety of operations that require breathing 100% oxygen. In addition, such a physiological marker would allow for more aggressive uses of HBO in the treatment of decompression sickness and various clinical HBO applications.

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Table 1. Minutes of notification prior to seizure latency for swine exposed to 3, 4, 5 and 6 ATA oxygen. Data expressed in mean ± SD.

Pressure (atm abs)	**MAP (min)**	**CBF (min)**
3	29.0 ± 19.2	49.1 ± 22.7
4	11.1 ± 6.8	18.4 ± 11.1
5	8.0 ± 6.0	11.4 ± 8.5
6	6.5 ± 3.8	8.3 ± 4.7